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Evaluation of tumor infiltrating lymphocytes in cutaneous and uveal melanomas; A histopathological and immunohistochemical study

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Abstract

Introduction: Cutaneous melanoma and uveal melanoma are derived from melanocytes with the same embryonic origin; however, their etiopathogenesis is very different. The presence of tumor-infiltrating lymphocytes (TILs) in melanoma is a kind of host's antitumor immunological response; however, the associations between the number of TILs and histopathological characteristics and tumor progression remain controversial.

Objectives: This study aimed to study the histological characteristics and immunophenotyping of both cutaneous and uveal melanoma affecting Egyptian patients where the melanoma is uncommon. Also, we tried to find the relationship between TIL amount and the tumor progression.

Patients and Methods: This is a cross-sectional study to assess the number (amount) and phenotype of TILs in 40 patients with cutaneous melanoma and seven patients with uveal melanoma using immunohistochemistry.

Results: The mean age of the cutaneous and uveal melanoma was 58.5±15 and 54.5±15 years, respectively, with no sex predominance. Tumor stage in cutaneous melanoma is associated with a decrease in TIL, whereas uveal melanoma has the opposite effect. The infiltrate was predominantly positive for CD3 and CD8, with minimal expression of natural killer (NK) cell markers. There is a significant difference between TIL and nodal metastasis in both types.

Conclusion: In this study we found an association between TIL amount and the tumor stage in both cutaneous and uveal melanomas with a significant difference between TIL infiltration and nodal metastasis. However, correlations between TILs and tumor progression should be further studied in different kinds of melanoma to aid in risk assessment and the prognostic significance of TILs in the rare eye tumor, uveal melanoma.

Introduction

Melanoma is the third most prevalent cutaneous malignancy; however, it is the most lethal when surgical treatment is neglected in the early stages (1,2). The incidence of melanoma is greatest in regions of lower latitude and among fair-skinned populations. Although melanoma is more common in elderly individuals, it is also among the most common tumors found in adolescents and young adults (2). Melanoma incidence also varies by sex, ethnicity, and region, with differences in anatomic site.

Ocular melanoma is a rare disease that largely affects the Caucasian population; it is the most prevalent primary intraocular malignancy in adults, with a mean incidence of 5.1 cases per million per year (age-adjusted rate). Ocular melanoma occurs in the iris (4%), ciliary body (6%), or uveal region (90%). Fair skin color, light eye color, difficulty tanning, ocular/oculodermal melanocytosis, iris or choroidal nevus, and BRCA1-associated protein 1 mutations are all risk factors for

Key point

- The relationship between the number of tumor-infiltrating lymphocytes (TILs)/histopathological characteristics and tumor progression remains controversial.
- We aimed to assess and correlate the TIL grade via the histological and IHC characteristics of both cutaneous and uveal melanomas from Egypt.
- The study found an association between tumor stage and the TIL amount, which was predominantly positive for CD3 and CD8, but minimal expression of NK cells (natural killer cells).
- Correlation between TILs and tumor progression should be further studied in different kinds of melanoma for assessment of the risk and the prognosis.

uveal melanoma (3).

In contrast to other malignant lesions, the presence of tumor-infiltrating lymphocytes (TILs) in uveal melanoma is associated with poor prognosis, but what regulates TIL infiltration and how TILs may promote progression has not yet been established (4).

According to clinical and preclinical studies on melanoma, examination of TILs by histopathologists has yielded many biological insights into tumor immunology, and several clinical centers have considered the therapeutic potential of TIL transfer in melanomas (5,6). Immune checkpoint blockade by anti-cytotoxic T-lymphocyte-associated protein 4 and/or anti-programmed cell death 1 (PD-1) is currently an effective therapy for late-stage cutaneous melanoma (7).

However, this clear antitumor immunological effect of TILs in primary melanomas and whether there are associations between the number of TILs and histopathological characteristics remain controversial (8,9).

Objectives

The aim of the present study was to assess and correlate the TIL grade via immunohistochemistry with the histological characteristics of both cutaneous and uveal melanomas surgically excised from patients in Egypt, where the lowest incidence rates of melanoma were reported in Africa and Asia.

Materials and Methods

This study is a cross-sectional study from Egypt. The authors obtained samples from various melanoma tissue blocks available in the pathology archives of Al-Azhar University, which were stored from 2010 until the end of 2023. The inclusion criteria included all cases of cutaneous and uveal melanoma with available paraffin blocks and related clinical data. The exclusion criteria included mucosal melanoma cases, cases diagnosed with incisional biopsies, and a lack of material and/or clinical data. The information, including age, sex, tumor size, skin lesion site, ocular lesion location, original sample, or metastasis, was extracted from the medical and pathological files and registered in the checklist of each sample.

A total of 47 melanoma cases were included: 40 cutaneous melanomas and seven uveal melanomas with available paraffin blocks. Sections with a thickness of 4–4.5 μm from the paraffin blocks were taken and stained with hematoxylin and eosin (H&E) and re-evaluated by histopathologists on site and remotely via telepathology.

Histopathologic typing of cutaneous melanoma was performed, with the consensus of at least three of the pathologists, according to the recent World Health Organization (WHO) classification. The 8th edition of the TNM system was adopted for histopathological staging (10). The depth of invasion was measured for the cases of cutaneous melanoma from the granular layer of the epidermis to the deepest point of invasion (in the case of ulceration, the depth started from the floor of the ulcer) (10,11). The adequacy of surgical excision was evaluated according to the shortest clearance of normal tissue (measured in mm) and correlated with tumor invasion (depth). 1-cm clearance is adequate in cases of 1-mm invasion (11), 2-cm clearance in cases of 2–4-mm invasion, and 5 cm invasion >4 mm (12).

To evaluate the immune response of the tissue, the TIL reaction was graded on H&E sections from all proven melanoma cases in the skin or ocular tissue via the three-tier pattern scheme, which is defined as follows: brisk pattern indicates lymphocytes present throughout tumor areas or in its advancing peripheral margin; non-brisk pattern reflects lymphocytes present only and focally in the tumor itself; and absent describes a situation in which lymphocytes are found only in the peritumoral stroma (13).

Immunophenotyping of cellular immunity was determined via CD3, CD8, and CD56 markers. Standard immunohistochemical methods and techniques were performed using the Dako autostainer (Dako, Carpinteria, California, USA) and Dako reagents. As a coloring agent, DAB chromogen was used, and hematoxylin was used as a counterstain. Quantitation of the targeted lymphocytes (count per mm^2) was performed via Leica photomicroscopy (Leica LAS image analysis, Wetzlar, Germany). Positive staining was counted in five random high-power fields at 40× magnification. The counts were averaged, with the following classifications applied: a score of + or 1 represents an average of 1-25 cells, ++ or 2 reflects 26-50 cells, and +++ or 3 indicates the presence of 51 or more cells in both the tumor and the stroma (9).

Statistical analysis

The collected data were analysed by version 26 of SPSS software and presented as mean ± SD or number and percent. Comparison between groups was conducted using $\chi 2$, or Fisher's test with respect to categorical data, as appropriate. All *P* values were two-sided, and less than 0.05 was considered significant.

Results

The baseline demographic and clinicopathologic

characteristics of all patients in this study are summarized in Table 1. The age of the patients with cutaneous melanoma ranged from 19-90 years with an average of 58.5 ±15 years and a minimally significant female predominance (the sex ratio of females to males was 1.1:1); however, the characteristics of patients with uveal melanoma differed (Table 1).

The most commonly affected sites were the head and neck, followed by the trunk. Lymph node metastases were evident in two-thirds of the cutaneous cases.

The most common histologic type was the nodular type (75% of all cutaneous cases) (Figure 1).

The pathological stages of cutaneous melanoma were as follows: 2 (5%) presented with stage I, 12 (30%) with stage II, and 26 (65%) with stage III. The TIL distribution in cutaneous and uveal melanoma patients can be seen in Table 2 and Figure 2, which shows the histological features and immunohistochemical expression.

The infiltrate is predominantly CD3 positive (T-phenotype) and cytotoxic T lymphocyte (CD8) positive, but NK cells (CD56 staining) are minimal in the infiltrate of all cutaneous cases and brisk positive in 2 (28.5%) uveal cases, non-brisk positive in 2 (28.5%), and negative in 3 (43%) eye specimens (Figure 3). The associations of melanoma risk factors with TIL grade are presented in Table 3. There was a significant difference between the age groups with respect to the number of TILs in cutaneous melanoma patients and the tumor thickness in both cutaneous and uveal melanoma patients; however, an increase in the tumor thickness (stage) of cutaneous melanoma patients was associated with a decrease in the number of TILs according to histology and CD3 and CD8 expression. Uveal melanoma patients presented the opposite trend. There was no significant difference in the number of TIL between male and female patients (Table 3).

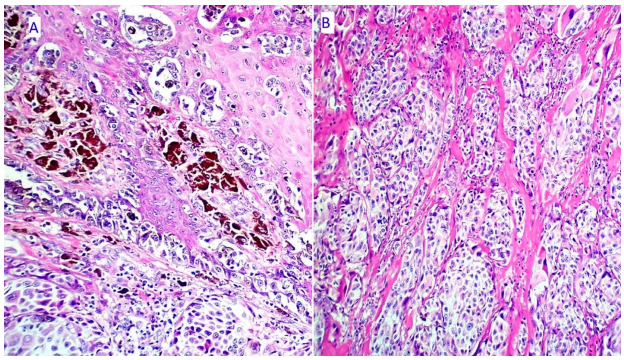

Figure 1. A histopathological picture of cutaneous melanoma, nodular type; a) tumor cells involving epidermis with marked pigmentation. b) malignant cellular features with scattered TIL (H&E, 200× original magnification).

Discussion

The therapeutic role of the TIL and its relationship with prognosis have been extensively studied in the aggressive melanocytic tumor melanoma (14).

TILs may encompass a range of immune cell subsets and their byproducts, which can either favorably or unfavorably impact tumor progression. In fact, accumulating evidence suggests that not only T cells but also natural killer (NK) cells, dendritic cells and macrophages can infiltrate

Table 1. Clinico-histological characteristics of both cutaneous and uveal melanoma cases

	Cutaneous melanoma			Uveal melanoma			*P* value
		N	%		N	%	
Age	Mean	58.5			55.4		>0.05[a]
	Average	19-90			29-81		
Sex	Male	19	47.5		4	57	>0.05[a]
	Female	21	52.5		3	43	
Site	Head and neck	30	75	Rt eye	5	71.5	
	Trunk	6	15				
	Upper limb	2	5	Lt eye	2	28.5	
	Lower limb	2	5				
Histological type	Superficial spreading	4	10	Epithelioid	0	0	
	Nodular	30	75	Spindle	3	43	
	Acral lentiginous	4	10	Mixed	4	57	
	Other	2	5				
Lymph node	Positive	26	65		4	57	<0.05[a]
	Negative	14	35		3	43	
Depth (mm)	0-1	2	5	Thickness (mm)	Mean	3.75	
	>1-2	4	10		Range	1-5	
	>2-4	8	20				
	>4	26	65				
Ulceration	Yes	26	65				
	No	14	35				

[a] χ^2 test.

Table 2. TILs distribution in cutaneous and uveal melanoma

	Cutaneous melanoma		Uveal melanoma	
	No.	%	No.	%
Brisk	3	7.5	3	42.5
Non-brisk	11	27.5	3	42.5
Negative	26	65	1	15
Total	40	100	7	100

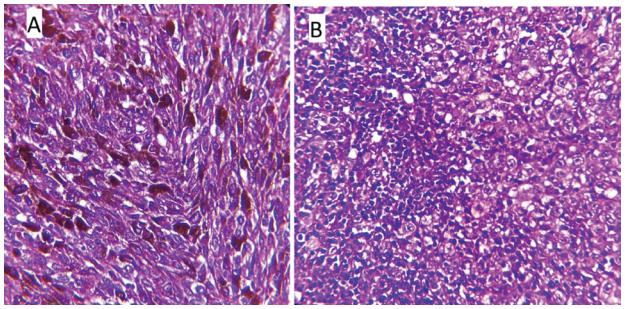

Figure 2. A histopathological picture of uveal melanoma; a) negative "absent" TIL (H&E, 400× original magnification), b) positive "brisk" TIL (H&E, 200× original magnification).

tumor tissues in variable amounts (15). Furthermore, the expansion of immunoregulatory immune cell subsets, such as regulatory T (Treg) cells and tolerogenic DCs, or alternative immune escape pathways operating in the tumor microenvironment may result in significant variations in TIL composition and immune effector functions. These factors emphasize the need to describe TILs both immunophenotypically and functionally to more precisely define TIL subtypes and TIL-specific immunoregulatory mechanisms that cause tumor regression in comparison to those described previously (15,16).

In this study, we detected lower expression of CD56 (an NK marker) in TIL infiltrates in both cutaneous and uveal melanoma; however, CD4+ and CD8+ T lymphocytes were both expressed and positively stained.

Correlations between TILs and tumor progression have been reported in several types of cancers, including colorectal and ovarian cancers, in addition to cutaneous melanomas (14,17,18). According to some authors, the presence of brisk T-cell infiltrates predicts improved survival in patients with metastatic melanoma to the lymph nodes compared with patients with lesions showing low or no TIL reactivity (14,19).

These findings indicate that the presence of TILs within a tumor can reflect the ability of the immune system to eliminate cancer. In support of this possibility, many decades ago, Clark and colleagues suggested that the radial growth phase in melanoma commonly evokes dermal lymphocytic infiltration to eliminate the tumor.

Our results from this study on Egyptian patients with cutaneous melanoma also support these findings; however, with respect to uveal melanoma, we found that TILs are associated with tumor thickness and increased tumor stage. However, other studies on melanoma patients did not find a significant effect of TILs on patient survival.

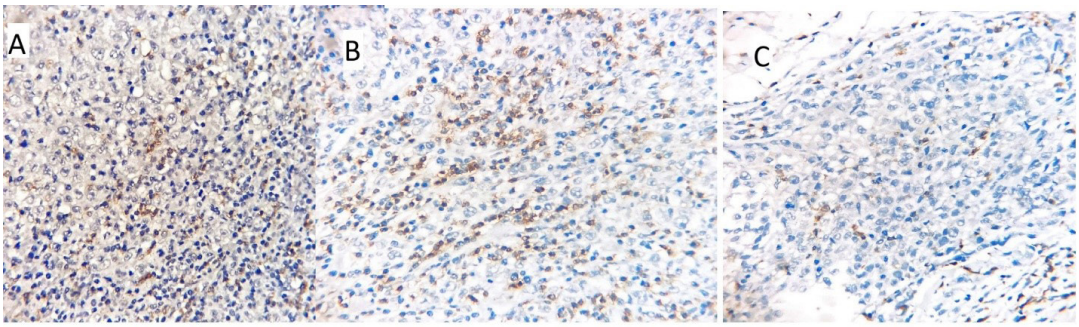

Figure 3. Immunophenotyping of TIL in melanoma; (a) positive CD3, (b) positive CD8, (c) scattered staining of CD56 (NK cells).

Table 3. Association analysis of TIL in both types with some parameters

Variable		Cutaneous melanoma			Uveal melanoma		
		+ve TIL (N)	-ve TIL	*P* value	+ve TIL (N)	-ve TIL	*P* value
Age	Old	8	1	<0.05	1	0	0.78
	Young or middle	5	26		5	1	
	Total number	13	27		6	1	
Gender	Male	6	15	>0.05	2	2	0.35
	Female	3	16		3	0	
	Total number	9	31		5	2	
Thickness	Low*	9	4	<0.05[a]	0	2	<0.05[b]
	High**	4	25		5	0	
	Total number	11	29		5	2	

*'low' shows <4 mm in cutaneous and <2 mm in uveal. **'High' indicates >2 mm in cutaneous and <2 mm in uveal melanoma.
[a] χ^2 test; [b] Fisher's test.

The proportion of affected patients who reported tumor recurrence was similar among the non-brisk and brisk TIL groups, but the pattern of recurrence was significantly different (14,20). With respect to uveal melanoma, our findings revealed that tumor thickness and advanced stage are associated with increased TILs.

Despite their shared origin, cutaneous and uveal melanomas have previously been shown to have different genetic profiles at their primary tumor sites (7). The incidence of uveal melanoma has remained stable over the last few decades, and cutaneous melanoma is 20–30 times more common than uveal melanoma (21).

Uveal melanoma is more common in lightly pigmented individuals and is infrequent in nonwhite individuals (21), with an average age at diagnosis of 62 years, according to several previous studies. This study of nonwhite patients revealed an average age of 55.5 years, with no significant difference between cutaneous and uveal melanomas (22-24).

The data in the literature concerning the correlation between TILs and tumor behavior in uveal melanoma are confusing and very difficult to understand (25,26). Some authors conclude that the presence of TILs in ocular melanomas does not guarantee a favorable prognosis or might even exacerbate the tumor rather than mitigate its progression (25).

In this study, we found that the TILs in both uveal and cutaneous melanomas were positive for both CD3 and CD8; however, there was less expression of CD56. For this reason, analysis of T-cell receptor S-chain expression may be beneficial for correctly interpreting the status and function of TILs in patients with melanoma.

Conclusion

This study included consistent histopathological and immunohistochemical analyses of TILs from patients from Egypt with cutaneous versus uveal melanoma. As a result, our findings demonstrate that lymphocytic infiltration is relatively increased in early-stage cutaneous melanoma; however, uveal melanoma has the opposite effect. There is a significant difference between TIL and nodal metastasis in both cutaneous and uveal melanomas. Given that there is not yet a consensus on the immunopathology or gold standard systemic treatment of uveal melanoma, early detection studies and advanced work on the etiopathogenesis of uveal melanoma are crucial.

Limitations of the study

The limitations of this study include the limited number of cases due to the rarity of disease in the Middle East, as well as the lack of genetic testing and inability to study its correlation with tumor survival due to lack of the required follow up data.

Authors' contribution

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Validation: Abdulkarim Hasan.
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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Al-Azhar University, Faculty of Medicine (Ethical code No. His_395_Med.Reserach_00000120). Prior to any intervention, all participants provided written informed consent. The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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